Remarks

Claims 8-13 are pending in the application with entry of the current amendment. Claim 14 is canceled herewith. Minor changes are made to claims to correct the spelling of "adsorption" and to correct antecedent basis errors (by use of "subject" to replace "patient").

A declaration of inventor Dr. Yaakov Naparstek is submitted under Rule 1.132 in connection with this response.

Rejections under 35 U.S.C. §103

Claims 8-14 are rejected under 35 U.S.C.§103(a) as being unpatentable over Gaubitz et al. (1993) ("Gaubitz") in view of U.S. 6,228,363 and Madaio et al. (1996). It is alleged to be obvious to combine the teachings of the '363 patent, which discloses that R38 is derived from laminin and is recognized by lupus antibodies (Madaio also discloses that laminin is recognized by lupus antibodies) with the teachings of Gaubitz, which describes immunoadsorption of a subject's plasma for removal of pathogenic antibodies.

Applicant respectfully traverses this rejection and will address some of the specific assertions presented in the office action.

1. It is asserted at page 2, under paragraph 5, that the Gaubitz reference "differs from the claimed invention *only* in that it does not teach a method employing a column comprising the R38 peptide nor the use of a Sepharose column". Applicant respectfully disagrees with this assertion, as it is not exactly correct. There are many significant differences between the method of the present invention and the disclosure of the references, and Gaubitz in particular.

Gaubitz discloses a comparison of two different immunoadsorption columns as treatment options for SLE. One of the columns uses phenylalanine, which removes antibodies by means of a non-specific

affinity. The other column, the Ig-Therasorb™ column, contains polyclonal sheep antihuman antibodies directed against immunoglobulin kappa and lambda light chains and IgG heavy chains. The size of the sheep antibodies bound to the column is 150,000Da and they bind the Fc portion of human antibodies present in plasma. Both columns provide non-specific removal of all antibodies in a patient's plasma, not just removal of pathogenic antibodies. As explained in a previous response, removal of all antibodies in a patient's plasma can result in a rebound effect.

In contrast, the R38 peptide is less than 3,000 Da in size, and binds only to lupus-specific antibodies, which are less than 1% of all antibodies present in an SLE patient's plasma. In the method of the present invention, the specific antibody-antigen (R38 – anti-R38 antibody) interaction is targeted in the separation column. This specific interaction is not shown in the two adsorption columns compared in Gaubitz, nor shown in any of the other adsorption columns described in Gaubitz at page 2, first column. Thus, the present invention differs from the teachings of Gaubitz in that 1) the specific R38 – anti-R38 antibody interaction is used as the basis for separation, 2) only lupus-specific antibodies are removed from plasma, 3) the size of the ligand on the column differs substantially from that shown in Gaubitz, and 4) the concentration of specific antibodies removed in relationship to the total concentration of antibodies in plasma is different.

2. It is further asserted in the Office Action at page 3, third paragraph, that "the extracorporeal column immunoadsorption of a subject's plasma for the removal pathogenic antibodies was known in the art", and that "substituting a ligand known to bind said pathogenic antibodies for the ligand of the primary reference would have been expected function for the binding and removal of said pathogenic antibodies from the plasma".

At the time of the present invention, there were no other methods of removing specific pathogenic antibodies via extracorporeal immunoadsorption known or commercially available for SLE. Thus, the statement that "removal of pathogenic antibodies was known" is not exactly correct; a more precise statement would be "in the context of SLE, removal of *all* antibodies from plasma was known".

Applicant agrees that in theory anti-R38 antibodies would be expected to bind to R38. However, as explained previously, there is no guarantee that the same binding shown on an ELISA plate will occur in a column, due to conformational changes in the protein when attached to a substrate. Moreover, the interaction of the plasma antibodies with the R38 peptides bound to the column occurs within less than three minutes during the flow of plasma on the 50ml column at a rate of 20ml/minute which is clearly different from incubation of plasma with the antigen in an ELISA plate which is performed for 30-60 minutes and in which there is no flow of the plasma antibodies.

One skilled in the art could not predict, based on the teachings of Gaubitz, that the specific R38 – anti-R38 antibody interaction would provide the basis for a successful method of treatment in SLE, given 1) the small size of the R38 protein, 2) possible changes in conformation due to binding on a substrate, 3) possible differences in antibody-antigen affinity of the R38-antiR38 antibody combination as compared to the sheep antibody/Fc system of Therasorb™, 4) the very low level of anti-R38 antibodies in plasma, and 5) the plasma flow rate required to make this method of treatment viable. It is Applicant's belief that the unpredictability of the entire system has been overlooked and unnoticed.

3. It is asserted in the Office Action that the data presented in the previous declaration are insufficient to show unexpected results, due to an alleged lack of statistical significance, among other things.

Applicant submits in connection with this response findings on ten additional patients. In seven of ten patients, a continued decline in anti-

R38 antibodies was observed one-month post-treatment; in three patients (see Figures 3, 6 and 7) no decline was observed. Thus, the unexpected result of a continued decline in antibody levels post-treatment has been confirmed in 7 out of 10 patients. Applicant knows of no case requiring a certain sample size to support a showing of unexpected results, and respectfully requests citation to such a case if the present showing is in any way inadequate. In any event, these results are, in fact, statistically significant ($p<.01$), as indicated in Figure 11 in the declaration.

It is further asserted in the Office Action that 1) there is no comparison to the closest prior art, and 2) there is no showing that the further decline in antibody levels is unexpected.

Regarding the first assertion, Applicant cannot compare the method of the present invention to "the closest prior art" because there is no prior art which shows removal of only lupus-specific antibodies in an immunadsorption column or removal of only lupus-specific antibodies from patient plasma by any other means. The Ig-Therasorb™ column removes all antibodies, as explained above; a comparison to this column would be of no probative value. The only comparison that would make sense, if it were possible, would be a comparison such as the one made in the Gaubitz paper, where two methods that use non-specific binding of antibodies are evaluated for their effects on SLE patients. Applicant would welcome any guidance the Examiner has to offer if a prior art teaching suitable for comparison has been overlooked.

Regarding the second assertion, basic scientific principles lead one to conclude that the results are unexpected: the plasma is passed through the column, and the column removes anti-R38 antibodies to a certain (lower) level. Absent the physical removal of the antibodies by the column, how is one to explain the continued decline in antibody levels? Again, Applicant would welcome any factual information that the Examiner can provide to explain this phenomenon; Applicant cannot

explain it himself. As with many other assertions in the Office Action, these are conclusory statements made without any factual foundation whatsoever. The continuing decline in antibody levels is indeed an unusual and unexpected result, one that could not have been predicted from the disclosure of any of the references cited, nor any reference known to Applicant. Applicant respectfully submits that any alleged *prima facie* case of obviousness has been overcome with evidence of unexpected results.

Finally, it is asserted in the Office Action that evidence of unexpected results must "properly appear in the specification" and can therefore be disregarded if not in the application as filed. Citation to *In re Davies and Hopkins*, 177 USPQ 381 (CCPA 1973) is provided as support for this position.

The Examiner's reliance on this case is far outside the mainstream of standard patent practice. A more recent case, reaching the opposite conclusion, is *Knoll Pharmaceutical Co. v. Teva Pharmaceuticals USA, Inc.*, 367 F.3d 1381, 1385, 70 USPQ2d 1957 (Fed. Cir. 2004), where the Federal Circuit stated ``There is no requirement that an invention's properties and advantages were fully known before the patent application was filed ... .''. Indeed, in *Knoll* the patentee was permitted to submit evidence of unexpected results at the time of trial to rebut the obviousness challenge.

As previously noted, evidence of unexpected results may be submitted in a declaration filed under Rule 1.132 during prosecution, as set forth in the MPEP Section 716. An entire section of the MPEP is devoted to this subject (declarations under 1.132). MPEP 716.01 states that "Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted prior to a final rejection" and in several other circumstances. This is also

set forth at MPEP Section 2141, Examination Guidelines for Determining Obviousness under 35 USC §103, where it is written,

> Objective evidence relevant to the issue of obviousness must be evaluated by Office personnel. *Graham v. John Deere Co.*, 383 U.S. at 17-18, 148 USPQ at 467 (1966). Such evidence, sometimes referred to as "secondary considerations," may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results. The evidence may be included in the specification as filed, accompany the application on filing, or be provided in a timely manner at some other point during the prosecution. The weight to be given any objective evidence is made on a case-by-case basis.

Accordingly, the Examiner is obligated to consider evidence of unexpected results submitted during prosecution.

Applicant submits that in view of the above comments, the differences between the invention and the prior art, and the evidence of unexpected results, any so-called *prima* facie case of obviousness has been overcome. Withdrawal of the §103 rejection is respectfully requested.

Rejection under 35 U.S.C. §112

The rejection of Claim 14 under 35 U.S.C. §112, first paragraph, is rendered moot by the cancellation of this claim.

Conclusion

Applicant submits that all outstanding issues have been addressed and that Claims 8-13 are in condition for allowance; such action is respectfully requested at an early date.

Respectfully submitted,

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